REMARKS

Applicants respectfully submit a request for continued examination under 37 C.F.R. § 1.114 in order to introduce the above claim amendments and following arguments. Applicants do not seek entry of the Amendment and Reply filed February 15, 2006.

1. Summary

The Office Action Summary reflects that claims 1, 2, 6, 7, and 48-67 are pending and stand rejected. The Summary also indicated that the drawings are accepted.

Applicants have amended claims 1, 6, 7, 48-60, 62-64, and 66-67. Applicants have cancelled claim 61. Support for the claim amendments are found at least in the claims as originally filed. Applicants have amended the claims to recite polypeptides, nucleic acids, and specified sequence identifiers. Applicants also have amended the claims to recite "reduce". The term is supported in the specification at least at page 20, lines 3-10. Accordingly, no prohibited new matter is believed to have been introduced by entry of the amendments, because the claims are supported at least by the claims as originally filed. Applicants have cancelled claim 61 and amended the claims without prejudice to or disclaimer of the cancelled subject matter. Applicants reserve the right to file a continuation or divisional application on any subject matter cancelled by way of this amendment.

2. Status of Prior Rejections

The Office states on page 2, second paragraph of the Office Action mailed November 15, 2005, that any rejections not reiterated in this action are withdrawn. Therefore, the rejections under 35 U.S.C. § 112, second paragraph of claims 2, 52, 54-57, and 61 on pages 3-4 stand withdrawn, as are the rejections under 35 U.S.C. § 112, first paragraph of claims 1, 2, 6, 7, and 48-61.

3. Information Disclosure Statements

Applicants note with appreciation that an acknowledged copy of the PTO Form 1449 submitted July 14, 2005 (4th Information Disclosure Statement) has been returned with the Advisory Action dated May 4, 2006.

Applicants submit herewith a new Information Disclosure statement and corresponding 1449 form. Applicants respectfully request acknowledgement of the form with the next Official paper.

4. Improper Final Rejection

Applicants' assertion that the finality of the rejection is mooted by the filing of the instant Request for Continued Examination.

5. Interest of Equity

Applicants will address the issue that arises under 35 U.S.C. § 154 at the appropriate time, as indicated by the Office.

6. Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 6, 7, and 67 stand rejected as indefinite, for the recitation of "the candidate molecule". Claim 67 depends from claim 6. Office Action dated November 15, 2006.

Applicants have amended claims 6 and 7 to remove "the candidate molecule" and to refer, as appropriate, to "the reagent", as suggested by the Examiner. The amendments to claims 6 and 7 (and thereby to claim 67) obviate the rejection pursuant to Office's admission in the Advisory Action dated May 4, 2006, Continuation Sheets, page 2. Accordingly, Applicants respectfully request withdrawal of the rejection and allowance of the claims 6, 7, and 67.

7. Rejection under 35 U.S.C. §§ 101 and 112, First Paragraph

Claims 1, 2, 6, 7, and 48-67 stand rejected under 35 U.S.C. §§ 101 and 112, first paragraph, because allegedly these claims are not supported by either a credible, substantial, and specific asserted utility, or a well-established utility for the reasons of record as stated in the Office Action dated February 24, 2005. Office Action, page 3 and Advisory Action, pages 2-6 of the Continuation Sheets. The Office in both the Office Action dated November 15, 2005, and the Advisory Action of May 4, 2006 base the crux of the rejection on two alleged points: (1) HBM and Zmax1 allegedly are not demonstrated to be involved with lipid regulation; and (2) a screening method using HBM and Zmax1 to identify molecules allegedly would result in molecules with no specific utility.

To the extent that the rejection applies to the claims as amended, Applicants traverse the rejection with the following argumentation.

7.1 HBM and Zmax1 Play a Role in Lipid Regulation

Applicants state in the specification that the genes are involved in lipid modulation. Humans with the HBM variant have an enhanced lipid profile, *e.g.* lowered levels of triglycerides and VLDL. *See e.g.,* Example 3 of the specification. Additionally, Zmax1 was shown at the time of filing to bind ApoE. *See e.g.,* pages 83-85, 115, and 125-128 of the specification.

Applicants also provided post-filing articles as data in support of what is stated in the specification. Applicants supply the following references, two of which are newly cited (*i.e.* references of Guo et al. and Suwazono et al.).

1). Y. Guo, et al., "*Polymorphisms of the Low-density Lipoprotein Receptor-related Protein 5 (LRP5) Gene are Associated with Obesity Phenotypes in a Large Family-based Association Study,*" __ J. MED. GENET ___ (2006).

2). Y. Suwazono, et al., "*G-protein Beta 3 Subunit Polymorphism C1429T and Low-density Lipoprotein Receptor-related Protein 5 Polymorphism A1330V are Risk Factors for Hypercholesterolemia in Japanese Males – a Prospective Study over 5 Years,*" 55 METABOLISM 751-7 (2006).

3). T. Fujino, et al., "*Low-density Lipoprotein Receptor-related Protein 5 (LRP5) is Essential for Normal Cholesterol Metabolism and Glucose-induced Insulin Secretion,*" 100 PROC. NAT'L ACAD. SCI. USA 229-234 (2003).

4). K. Magoori et al., 2003 "*Severe Hypercholesterolemia, Impaired Fat Tolerance and Advanced Atherosclerosis in Mice Lacking Both LDL Receptor-related Protein 5 (LRP5) and Apolipoprotein E,*" 278 J. BIOL. CHEM. 278: 11331-11336.

5). S. Q. Ye et al., "*Influence of Genetic Polymorphisms on Responsiveness to Dietary Fat and Cholesterol,*" 2000 AM. J. CLIN. NUTR. 72: 1275S-1284S.

These references, when taken alone or together, demonstrate that LRP5 (a synonym for a wild type form of Zmax1) has a role in meditating lipid levels. Applicants provide the HBM variant and show that humans expressing the variant have an enhanced lipid profile. The Suwazano reference identifies a detrimental polymorphism in LRP5 that causes hyperlipidemia in affected individuals. Guo makes the statement "[p]olymorphisms of the low-density lipoprotein receptor-related protein 5 (LRP5) gene are associated with obesity phenotypes in a large family-based association study." *See* Abstract. Here the authors begin in their abstract by stating: "LRP5, essential for glucose and cholesterol metabolism, may play a role in etiology of obesity, an important risk factor for diabetes." *Id.* The authors make the point that LRP5 is essential for cholesterol metabolism. The reference again supports Applicants asserted utility in the application.

The remaining references of Fujino, Magoori, and Ye have been previously discussed in the record. The references are cumulative evidence in evincing that LRP5/Zmax1 regulates lipid levels, contrary to the Office's assertions.

The fact that lipid regulation may be complex or that the role of Zmax1 and HBM may not be fully elucidated with regard to all the other players in lipid regulation does not negate their role in lipid regulation. Accordingly, HBM/Zmax1 can be used as a target in drug screening. The claimed methods provides for methods of identifying binding reagents and determining those reagents that bind HBM/Zmax1 that further lower a lipid level (as amended).

Therefore, as set forth in MPEP § 2107.01 (I)(C)(Research Tools), this is a screening assay which has specific utility as an assay for screening compounds that lower a lipid level.

7.2 Molecules Identified by the Screening Method Have A Specific Utility

The claimed screening method would serve to screen libraries of compounds to identify subgenuses and species of compounds that reduce lipid levels. Such a screening assay has a specific utility as set forth in MPEP § 2107.01.

Applicants distinguish the instant claims from the facts set forth recently in *In re Fisher,* 76 U.S.P.Q.2d 1225 (Fed. Cir. 2005). In *Fisher*, the Court found that utility was lacking in a method of screening assay that used ESTs to identify polymorphisms in plants, wherein the identified polymorphism would have no characterized feature. In contrast, Applicants are using fully isolated sequences, which have had human genetic analysis performed on the patient populations expressing the normal and HBM variants for both bone regulation and lipid profiles. The screening methods presently claimed are to identify compounds that have lipid regulating capability. Their identification as (1) binding Zmax1 and/or HBM, and (2) lowering a lipid, provides a method of identifying drug candidates. The screening methods are research tools. They therefore have utility.

Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 101 for lack of utility.

7.3 The Method of Screening is Enabled

The utility rejection is combined with a rejection of lack of enablement under § 112, first paragraph. Applicants traverse the rejection and address it to the extent it applies to the amended claims.

The claimed methods involve, as discussed above, a binding step and analysis of whether a reagent that binds to HBM/Zmax1 induces a change in a lipid level *in vivo* or in a cell assay. All the reagents were known or are provided. Binding assays for nucleic acids and polypeptides were known at the time of filing as discussed in the record. Methods of assessing lipid changes *in vivo* and in cell assays were also known at the time. For example, dietary regimens in rabbits were known. Animal models exist for familial hypercholesterolemia. *See, e.g.,* T. Kita et al., "*Probucol prevents the progression of atherosclerosis in Watanabe heritable hyperlipidemic rabbit, an animal model for familial hypercholesterolemia,*" 84 PROC. NAT'L ACAD. SCI. USA 5928-5931 (1987). Alternatively, animal models can be transgenic models with specific genes knocked out like those of Magoori et al. (2003). Lipid analysis can be performed using various diets followed by blood testing of the subject, whether human or non-human. *See, e.g.*, the diet and tests used to analyze obtain angiographic

measurements, histological measurements, cell culture studies, and lipoprotein and plasma cholesterol levels using the New Zealand White rabbit model of atherosclerosis induced by femoral air desiccation with a high cholesterol diet. A. M. Lafont et al., "*Effect of Alpha-tocopherol on restenosis after angioplasty in a model of experimental atherosclerosis*," 95 J. CLIN. INVEST. 1018-1025, at 1018-1020 (1995). Thus, the various methods for detecting lipid levels, changes in lipid levels, and changes in lipid ratios were known in the art at the time. As a skilled artisan would have known how make and use the claimed screening methods, because no undue experimentation is required. The experimentation is the method of carrying out the claims. Thus the claims as amended or previously presented are enabled.

7.4 The term "modulation" is clear

Applicants maintain that the term "modulating" and "modulation" is clear on its face given what a skilled artisan would have understand it to mean. *See, e.g.*, specification on page 20, lines 3-10. In order to further prosecution, Applicants have amended the claims to recite "reduce a lipid".

To the extent that the rejection under 35 U.S.C. §§ 101 and 112, first paragraph flowed from "modulates", the rejection is mooted and should be withdrawn.

For all the reasons stated above, Applicants respectfully request that the combined rejection under 35 U.S.C. §§ 101 and 112, first paragraph be withdrawn, and the claims allowed.

8. Rejection under 35 U.S.C. § 112, First Paragraph

Claims 1, 2, 6, 7, and 48-67 remain rejected under 35 U.S.C. § 112, first paragraph for allegedly failing to comply with the enablement requirement for the reasons of record as set forth in the Office Action mailed February 24, 2005. *See* Office Action, pages 3-4 and Advisory Action, Continuation Sheets pages 6-9.

The crux of the Office's position as stated in the Advisory Action is that "additional experimentation would be required because the mere binding of a reagent to Zmax1/HBM would not be indicative as to which, if any, of the multiple pathways the reagent would affect." Advisory Action Continuation Sheets, page 9. To the extent this issue remains for the claims as amended, Applicants traverse the rejection.

Enablement requires that the skilled artisan at the time of filing be able to make and use the invention as claimed. The screening method involves first finding a reagent that binds to a HBM/Zmax1 polypeptide or nucleic acid. If the reagent binds, the next step is determining whether the reagent modulates a lipid. Screening compound libraries was known at the time. Applicants

provide the sequences of HBM and Zmax1 combined with the determination that these sequences regulate lipids. Assays for both screening changes in lipid levels *in vivo* and in cell assays *in vitro* were known at the time. Accordingly, contrary to the Office's assertion, no further experimentation, which apparently would be undue experimentation, would have been required at the time to make and use the claimed methods.

The Office asserts that additional experimentation would be required to elucidate which of the multiple pathways the reagent would affect. Applicants disagree that the claims for enablement require an additional step. If the reagent reduces a lipid, further elucidation of the pathway involved is not required in order to make and use the claimed method.

Thus, for at least these reasons, Applicants assert that the *prima facie* case of lack of enablement should be withdrawn and the claims allowed.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

If any fees are required, or if a Notice of Appeal fee (and associated Notice of Appeal) is required to maintain pendency, the Office is asked to charge Deposit Account No. 50-0573. The Office can credit any overpayments to the Account.

Respectfully submitted,

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